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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020287/S008

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

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ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

FRAGMIN®
(dalteparin sodium)
INJECTION

NDA 20-287/S-008

Division of Gastrointestinal and Coagulation Drug Products
HFD-180
Food and Drug Administration
Center for Drug Evaluation and Research

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FINDING OF NO SIGNIFICANT IMPACT

NDA 20-287/S-008
Fragmin® (dalteparin sodium) Injection

A new indication, thromboprophylaxis in patients undergoing hip replacement surgery.

The National Environmental Policy Act of 1969 (NEPA) requires all federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center of Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Fragmin® Injection, Pharmacia & Upjohn Company has prepared an environmental assessment in accordance with 21 CFR 25.31a(b)(5) which evaluates the potential environmental impacts of the manufacture, use, and disposal of the drug product.

In support of their supplemental new drug application (SE1-008), Pharmacia & Upjohn & Upjohn Company has referenced the original EA and provided the following important additional revision to the NDA EA:

> A new indication, Fragmin Injection for thromboprophylaxis in patients undergoing hip replacement surgery.

The new EA information does present new information on the manufacture of dalteparin sodium in that dalteparin is a depolymerized heparin (from porcine intestinal mucosa) obtained by sodium nitrite oxidation followed by sodium borohydride reduction. The Fragmin® Injection information remains the same with respect to the formulation.

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Approval of the supplemental application will make prophylactic therapy available to a larger group of patients as reflected in the revised indication:

> FRAGMIN® Injection is indicated for prophylaxis against deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing hip replacement surgery. FRAGMIN® is also indicated for prophylactic use in abdominal surgery patients at risk for thromboembolic complications.

The drug product will be used in hospital settings for in-patient and out-patient treatment. Disposal is by hospitals as medical waste and returned or damaged product as medical/hazardous waste. The fate and effects of dalteparin sodium remain unchanged from the original EA. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

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July 18, 1997
DATE

/S/

PREPARED BY:
Joseph Sieczkowski, Ph.D.
Review Chemist
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Office of New Drug Chemistry II, HFD-820

7/22/97
DATE

/S/

DIVISION CONCURRENCE:
Eric P. Duffy, Ph.D.
Chemistry Team Leader
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Office of New Drug Chemistry II, HFD-820

7/26/97
DATE

/S/

APPROVED:
Nancy B. Sager
Environmental Scientist, HFD-357
Center for Drug Evaluation and Research

Attachment:
Enviromental Assessment Material Safety Data Sheet (Drug Substance).
Environmental Assessment FOI version.

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ENVIRONMENTAL ASSESSMENT REPORT (EA)

This Environmental Assessment is being submitted in accordance with the requirements of 21 CFR 25.31a(b)(5) to accompany Pharmacia & Upjohn Company's (P&U) supplemental New Drug Application (NDA) #20-287 for FRAGMIN® (dalteparin sodium) Injection.

1. DATE

March 1992
Revised: June 1997

2. NAME OF APPLICANT

Pharmacia & Upjohn Company

3. ADDRESS

The mailing address and telephone number of P&U's Kalamazoo site are:

7000 Portage Road
Kalamazoo, Michigan 49001

Corporate telephone number (616) 833-4000

4. DESCRIPTION OF THE PROPOSED ACTION

4.a. Requested Approval

The former Kabi Pharmacia AB filed NDA #20-287 in October 1991 pursuant to Section 505(b) of the Food, Drug and Cosmetic Act for FRAGMIN® (dalteparin sodium) Injection.

The drug substance is packaged in polyethylene bags enclosed in aluminum foil. The drug product will be marketed in the U.S. in single-dose syringes of [redacted] with a needle of passivated stainless steel. A needle shield [redacted] plunger stopper [redacted] and a plunger [redacted]

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The drug product, FRAGMIN (dalteparin sodium) Injection 2500 IU (anti-X_a)/0.2 mL and 5000 IU (anti-X_a)/0.2 mL, will be marketed in the U.S. as 10-packs of single-dose syringes.

4.b Need for Action

- Indication

The original EA dated 1 March 1992 covered the indications of both abdominal surgery and hip replacement surgery; however, the hip replacement surgery indication was later withdrawn from that NDA.

This supplement to NDA #20-287 is intended for hip replacement surgery.

- Action Mode

Please see Item 4, Description of proposed action, p. 406, of the original EA, included as non-confidential Appendix 1. A Finding of No Significant Impact (FONSI) was issued for this EA on 3 March 1993 (copy attached as non-confidential Appendix 2).

4.c Production Locations

- Drug Substance - Sweden

All steps involved in manufacturing, processing, packaging, labeling and control operations of the drug substance are performed by Pharmacia & Upjohn AB at the following sites:

The [redacted] drug substance is performed at:

Pharmacia & Upjohn AB
Mariefredsvägen 37
S 645 41 Strängnäs, Sweden

Control laboratories for testing raw materials, packaging materials, intermediates and finished product are located at:

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Pharmacia & Upjohn AB
Lindhagensgatan 133
S 112 87 Stockholm, Sweden

Pharmacia & Upjohn AB
Nordenflychtsvägen 62
S 112 87 Stockholm, Sweden

The plant site is near the town of Strängnäs, 80 kilometers southwest of Stockholm. This plant is Pharmacia & Upjohn's main facility for production of substances by biochemical and chemical processing.

The site is [redacted]. The areas of buildings are [redacted] The plant consists of approximately [redacted] buildings for chemical and biochemical production, storage, utilities, laboratories, offices and waste water treatment. It is located in an industrial area outside the town. The surrounding area is flat and rural.

- Drug Product - Germany

All steps involved in manufacturing, processing, packaging, labeling and in-process controls of the drug product will be performed at Pharmacia & Upjohn's contract manufacturer, [redacted] All analyses specified by the drug product specifications are performed by Pharmacia & Upjohn in Sweden, except for the sterility test and ejectable volume, which are performed at [redacted] at the following address:.

[redacted]

The plant site is located in [redacted], a town in southern [redacted] produces mostly sterile drug products and works exclusively as a contract manufacturer. The manufacturing site is located in an industrial area on the outskirts of the town.

4.d Locations of Use

The ultimate use and disposal of the finished product will be mainly at hospitals, clinics, and consumer dwellings. Finished products will be stored in distribution centers throughout the U.S. prior to transportation for sale at hospitals, clinics, and pharmacies.

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4.e Disposal Sites

Disposal of drug product may result in the form of rejected, expired, or returned goods or from end user disposal of individual units of empty or partly empty finished product containers. Recovery and/or ultimate disposal mechanisms follow:

- Rejected, Expired or Returned Drug Product

Rejected, expired, or returned drug product will be disposed in the on-site permitted incinerator at the P&U Kalamazoo, Michigan site.

- *On-Site Incinerator.* The incinerator is being operated as a Resource Conservation and Recovery Act (RCRA) interim status treatment facility under EPA I.D. #MID000820381 in compliance with 40 CFR 265, Subpart O requirements.

A hazardous waste RCRA Part B/Act 451, Part 111 permit application has been submitted to the Waste Management Division of the Michigan Department of Natural Resources (now the Michigan Department of Environmental Quality , MDEQ) in Lansing, Michigan. The P&U facility is operating under interim status provisions until action is taken on the permit application. MDEQ action on the permit application is expected in 1997. The State air permit issued on July 15, 1980 (#242-80), revised to incorporate the Act 451, Part 111 requirements, was approved on May 26, 1993.

The incinerator is a two-stage system: the primary chamber rotary kiln operates at a minimum of 700°F; the secondary chamber, where final destruction of the product and off-gasses occurs, operates at a minimum of 1,904°F. The incinerator is equipped with a pollution control equipment train designed to remove gaseous and particulate pollutants. The pollution control equipment consists of: a quench section, an acid-gas pre-scrubber, a Venturi scrubber, an entrainment separator, an induced draft fan, and an exhaust stack.

All necessary permits are in place for the manufacture of this product to begin, as an existing interim status facility in accordance with Section 3005(e) of RCRA and Michigan Act 451, Part 111 licensing requirements.

Ash generated as a result of the incineration process is sent to a permitted hazardous waste landfill. At the present time, P&U has available for use the following facilities:

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- *Hazardous Waste Landfills:*

  - Environmental Quality Co., 1349 South Huron Street, Ypsilanti, MI: Michigan Disposal, Inc., 49350 North I-94 Service Drive, Belleville, MI (treatment) operating license listed under EPA ID No. MID 000 724 831; Wayne Disposal, Inc., 49350 North I-94 Service Drive, Belleville, MI (disposal) operating license listed under EPA ID No. MID 048 090 633;

  - Chemical Waste Management of Indiana, Inc., 4636 Adams Center Road, Fort Wayne, IN, operating license listed under Indiana Dept. of Environmental Management (IDEM) Permit No. IND 078911146;

  - P&U may use other facilities for such disposal which are suitable for that purpose and are properly permitted.

P&U has contracts with each of these facilities that require the facility to be in compliance with all applicable laws and regulations. The waste stream profile support documentation established with the hazardous waste landfill sites affirm compliance status. All facilities are audited and approved for use by a P&U environmental auditor prior to the first shipment of waste from P&U to the site. In addition, P&U personnel conduct periodic environmental audits of off-site disposal facilities during use of the facilities.

- Discarded Product in Hospital, Clinic Setting, or Consumer Dwelling

  - Any discarded product or product containers generated in a hospital or clinic environment will typically be disposed in accordance with applicable Federal, State and local regulations governing hospital wastes.

  - Individual empty or partly empty end products disposed by consumers will be handled along with household garbage by the community's solid waste management system and disposed in an approved sanitary landfill. Only minute traces of the active ingredient, dalteparin sodium, would be expected to remain with empty product containers.

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5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THIS PROPOSED ACTION

- **Drug Substance**

The materials used in processing the drug substance, dalteparin sodium, including Chemical Abstracts Service (CAS) No., molecular weight (M.W.), empirical formula, and a brief physical description, are included in confidential Appendix 7. [not included in FOI document]

- **Drug Product**

The material safety data sheet (MSDS) for the drug product, FRAGMIN, is enclosed as non-confidential Appendix 3. The ingredients used in formulating the drug product, FRAGMIN (dalteparin sodium) Injection, including Chemical Abstracts Service (CAS) No., molecular weight (M.W.), empirical formula, and a brief physical description, are included at non-confidential Appendix 4.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The drug product is not expected to be introduced into the environment through transportation and storage. Product will be shipped in Department of Transportation (DOT) specification packaging. FRAGMIN (dalteparin sodium) Injection is not regulated as a hazardous material under current DOT regulations. Product ready for shipment will be stored in either the manufacturing facility or distribution centers. Both maintain security through limited access.

6.a Substances Expected to be Emitted

A list of substances that may be emitted during the synthesis of the drug substance and drug product are included at confidential Appendix 7 [not included in FOI document] and non-confidential Appendix 4.

6.b Controls Exercised

Certifications from responsible company officials that the drug substance synthesis plant and drug product manufacturing plant are in compliance with, or on an enforceable schedule to be in compliance with, all national, regional, provincial and local environmental laws and regulations and all emission limits, permits and consent decrees are provided in non-confidential Appendices 5 and 6.

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6.c. Rejected, Expired or Returned Drug Product

Section 4. includes a discussion of any rejected, expired or returned drug product that would be disposed through the P&U Kalamazoo, MI site.

6.d Citation of and Statement of Compliance with Applicable Emission Requirements

- Disposal Site - Kalamazoo, MI

The following regulations or standards are cited as applicable to the proposed action:

1. Federal Food, Drug and Cosmetic Act, PL 75-717, as amended, including subsections 306(a) and (b) [debarment].
2. Clean Air Act PL 91-604, as amended.
3. Clean Water Act PL 95-217, as amended.
4. Safe Drinking Water Act PL 93-523.
5. Resources Conservation and Recovery Act of 1976 PL 94-580, as amended.
6. Occupational Safety and Health Act of 1970, as amended.
7. Hazardous Materials Transportation Act of 1975, as amended.
8. Standards from the American National Standards Institute.
9. National Fire Protection Agency Standards.
   a. National Electrical Code Standards
   b. Life Safety Requirements
10. Act # 451 of 1994, Michigan Natural Resources and Environmental Protection Act, as amended including:
    - Part 31, Water Resources Protection
    - Part 55, Air Pollution Control
    - Part 111, Hazardous Waste Management
    - Part 115, Solid Waste Management
    - Part 121, Liquid Industrial Waste
    - Part 625, Mineral Wells
11. Act #399 of 1976, Michigan Safe Drinking Water Act, as amended.
12. Act #368 of 1978, Public Health Code.
13. Chapter 28 of the Kalamazoo City Code (Services and Wastewater) as amended by ordinance No. 1190.
14. Michigan Occupational Safety and Health Act of 1970, as amended. (Local regulation applicable to the State of Michigan.)

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- *Emission Requirements.* P&U states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees or administrative orders applicable to the disposal of dalteparin sodium at its facilities in Kalamazoo, Michigan, as well as emission requirements set forth in applicable Federal, State, and local statutes and regulations applicable to the disposal of dalteparin sodium at its facilities in Kalamazoo, Michigan.

- *OSHA Requirements.* P&U certifies that it has comprehensive programs and practices in place addressing all applicable OSHA requirements.

6.e. Discussion of the Effect of Approval on Compliance with Current Emissions

The approval of the FRAGMIN (dalteparin sodium) Injection supplemental NDA will have no effect on the ability of P&U sites to meet their current emission requirements.

6.f. Expected Introduction Concentrations (EIC)

A theoretical EIC for the aquatic environment can be calculated for dalteparin sodium utilizing the following equation and fifth-year production estimates. (See confidential Appendix 8 for the five-year market forecast.) [not included in FOI document]

EIC-aquatic (ppm) = A x B x C x D

where:

A = kg/year production
B = 1/liters per day entering POTWs*
C = year/365 days
D = [redacted]

[redacted]

CDER has routinely found that drugs at concentrations [redacted] have no significant effect on relevant standard test organisms and therefore are unlikely to have a significant effect on the environment. CDER has also determined that information for environmental assessment format items 7, 8, 9, 10, and 11 will normally not be needed whose expected introduction concentration is [redacted] Since the calculated EIC for FRAGMIN at its highest manufacturing rate in the next five years is [redacted] (the actual figures are presented in confidential Appendix

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8) [not includeded in FOI document], the format items mentioned above have not been included.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Based on information in CDER's revised guidance document dated November 1995 (see Guidance, Section 14.) wherein FRAGMIN meets the Tier 0 criteria, information for format items 7 through 11 are not included for this document.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Based on information in CDER's revised guidance document dated November 1995 (see Guidance, Section 14.) wherein FRAGMIN meets the Tier 0 criteria, information for format items 7 through 11 are not included for this document.

9. USE OF RESOURCES AND ENERGY

Based on information in CDER's revised guidance document dated November 1995 (see Guidance, Section14.) wherein FRAGMIN meets the Tier 0 criteria, information for format items 7 through 11 are not included for this document.

10. MITIGATION MEASURES

Based on information in CDER's revised guidance document dated November 1995 (see Guidance, Section 14.) wherein FRAGMIN meets the Tier 0 criteria, information for format items 7 through 11 are not included for this document.

11. ALTERNATIVES TO THE PROPOSED ACTION

Based on information in CDER's revised guidance document dated November 1995 (see Guidance, Section 14.) wherein FRAGMIN meets the Tier 0 criteria, information for format items 7 through 11 are not included for this document.

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12. LIST OF PREPARERS

The following persons contributed to the preparation of this EA:

Anders Måhl	Environmental Coordinator Environment & Safety, Stockholm Pharmacia & Upjohn AB M.S., Chemical Engineering Professional experience: 27 years
Jeffrey S. Mehring	Manager, Science & Information Environment & Safety Pharmacia & Upjohn Company Ph.D., Agriculture Professional experience: 26 years
Susan I. Shedore	Environment & Safety Environmental Technician Pharmacia & Upjohn Company A.A. Corporate experience: 26 years

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13. CERTIFICATION

The undersigned officials certify that the information presented is true, accurate, and complete to the best of their knowledge.

The undersigned officials certify that the EA summary document and Appendices 1-6 contain non-confidential information and acknowledge that this information will be made available to the public in accordance with 40 CFR § 1506.6.

Randal S. Senger

June 9, 1997

Randal S. Senger, Associate Director
Environment and Safety
(telephone 616/833-5341)

Date

Jeffrey Mehring

9 JUNE 97

Jeffrey S. Mehring, Manager
Science and Information
Environment and Safety
(telephone 616/833-4746)

Date

14. REFERENCES

1992 Needs Survey, Report to Congress, EPA 832-R-93-002, September 1993.

Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements. Center for Drug Evaluation and Research, CMC 6, November 1995.

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15. APPENDICES

Non-Confidential

1 Original EA for FRAGMIN dated 1 March 1992
2 Finding of No Significant Impact (FONSI) dated 3 March 1993 written for original EA for FRAGMIN dated 1 March 1992
3 MSDS for the Drug Product, FRAGMIN
4 Ingredients Used in Formulating the Drug Product
5 Compliance letter - Sweden
6 Compliance letter - Germany

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NON-CONFIDENTIAL APPENDICES

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Freedom of Information Document

Non-Confidential
Appendix 1

Original EA dated 1 March 1992

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Environmental assessment for proposed approvals of FDA-regulated products-Format 1 as per 21 CFR 25.31a (b)(5).

Item 1.) Date; March 1, 1992

Item 2.) Applicant Name; Kabi Pharmacia, AB

Item 3.) Address:

Corporate office; Rapsgatan 7
S-751 82 Uppsala
Sweden

Division headquarters, R and D, and Manufacturing site;

Lindhagensgatan 133
S-112 87 Stockholm
Sweden

Item 4.) Description of proposed action;

The applicant is requesting approval of its' New Drug Application for the use of a low molecular weight heparin, call Fragmin®, as prophylaxis against thromboembolic complications in the peri- and post operative period of surgery. Because Fragmin acts mainly by accelerating the rate of neutralization of certain activated coagulation factors by antithrombin (other mechanisms may be involved) it is considered an antithrombotic. By its binding to antithrombin it potentiates, preferentially the inhibition of coagulation Factor Xa and only slightly affects thrombin inhibition and clotting time. The antithrombotic effect of fragmin is well correlated to the inhibition of Factor Xa. As such, a single daily injection of 2500IU (anti Factor Xa) of Fragmin can significantly reduce the incidence of thromboembolic complication of general surgery. A single daily injection of a higher dose, 5000IU (anti Factor Xa), significantly reduces thrombosis in orthopedic surgery, and in the surgical treatment of patients with malignant disorders and or other risk factors considered to increase the thrombosis risk. Thus the resultant reduction of thromboembolic complications such as deep vein thrombosis and pulmonary embolisms could lead to reduction in death from these causes as well as from myocardial infarction.

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The product will be produced at the following sites in Sweden and Germany;

Manufacturer of Fragmin Drug Substance:

All steps involved in the manufacturing, processing, packaging, labeling and control operations are performed by Kabi Pharmacia AB, Sweden in its' own facilities at the following sites:

The degradation of heparin sodium, isolation and purification of the drug substance is performed at;

Kabi Pharmacia AB, Mariefredsvägen 35, S15200 STRÄNGNÄS, Sweden.

Control laboratories for testing raw materials, packaging materials, intermediates and finished product are located at;

Kabi Pharmacia AB, Lindhagensgatan 133, S11287 STOCKHOLM, Sweden.

Kabi Pharmacia AB, Nordenflychtsvägen 62, S11287 STOCKHOLM, Sweden.

Control laboratories for biological test are located at;

Kabi Pharmacia AB, Franzéngatan 7, S11287 STOCKHOLM, Sweden.

Kabi Pharmacia AB, Kraftvägen 1, S19634 KUNGSÄGEN, Sweden.

Manufacturer of Fragmin Drug Product:

All steps involved in the manufacturing, processing, packaging,labeling and in-process controls are performed at Kabi's contract laboratory, [redacted] All analyses specified by the Drug Product Specifications are performed by Kabi Pharmacia in Sweden, except for the sterility test and ejectable volume, these are done at Vetter.

Manufacturing facility:

[redacted]

Labeling and Packaging:

[redacted]